Remarks

This paper is being submitted in response to the November 30, 2004 Office Action. Per the petition and fee submitted herewith, the Applicants hereby extend the deadline for responding by two month to April 30, 2005. No further fee is believed due for the filing of this amendment. However, if a response is due, please charge deposit account no. 50-2719.

Claims 42, 43, 61 and 62 are pending in the application. By operation of this amendment, claim 42 has been amended claim 43 has been cancelled. New claims 63 and 64 have been added.

Support for amended claim 42 is found in the specification on page 7, lines 13-15 and page 22, line 2. Support for new claim 63 is found in the specification on page 22, line 2. Support for new claim 64 is found in the specification on page 56, lines 13-21. No new matter has been added by these amendments.

Based on the above changes and the following remarks, the Applicants respectfully request reconsideration of the claims.

Restriction Requirement

The Applicants confirm the election, without traverse, of the claims of Group I (claims 42, 61 and 62). Claim 42 as amended, and new claims 63 and 64 are directed to processes for treating or reducing fibroses. Thus, claim 42 as amended and new claims 63 and 64 fall within the scope of the elected invention.

Objections to the Specification

A title that is clearly indicative of the invention to which the claims are directed has been added, as requested by the Examiner.

The specification has been amended to correct an obvious error in the representation of the units for molecular weight; *e.g.*, "g/mole^{-1}" has been replaced with "g/mole" on page 37, lines 19 and 27; page 38, lines 16-17 and 20-21; and page 39, lines 3, 8 and 12. No new matter has been added by these amendments.

Drawings

A replacement drawing sheet for Figure 15 has been submitted, in which "Percentage of FGF2 and FGFβ . . ." has been corrected to read "Percentage of FGF2 and TGFβ . . ."

Regarding the objections to Figs. 19 and 27-29, the Applicants respectfully point out that 30 sheets of formal drawings were submitted with the filing of this application on October 28, 2003; these were called "Replacement Drawings" in the transmittal letter provided with this application as filed. These Replacement Drawings replaced the informal drawings filed with the parent application 09/765,788 filed on January 19, 2001. Fig. 19 of the Replacement Drawings does not contain the French word "rien," and Figs. 27-29 of the Replacement Drawings are believed to be clear and legible. The Applicants respectfully request that the Examiner locate the Replacement Drawings and use these (except for Fig. 15 as provided herein, and Figs. 12, 13 and 16 filed on February 20, 2004) as the formal drawings for the case, as was originally intended.

Response to section 112 rejections

Claims 42 and 61-62 are rejected under 35 U.S.C. 112, 1st paragraph as allegedly being non-enabled for treating fibroses with AXY polymers other than AXY polysaccharide polymers. The Applicants respectfully disagree. However, in the interests of advancing prosecution, claim 42 has been amended to specify that A in the claimed AXY polymers is a monomer selected from the group consisting of a sugar or -(O-CH_2-CH_2-CO)-. New claim 63 has been added which specifies that the sugar is glucose.

To be enabling, a specification must teach one skilled in the art how to make and use the claimed invention without undue experimentation. Here, the specification teaches in Example 1, beginning on page 22, how to synthesize AXY polymers wherein :

- A is -(O-CH_2-CH_2-CO)-;
- X is -COOH or –COO^-Na^+; and
- Y is -CO-CH_2-CHOH-CH_2-SO_3H or -CO-CH_2-CHOH-CH_2-$SO^{3-}Na^+$.

Example 2, beginning on page 29, shows the synthesis of AXY polymers wherein:

- A is a glucose,
- X is -COOH or –COO^-Na^+
- Y is -SO_3H or -$SO^{3-}Na^+$.

The Applicants respectfully submit that one skilled in the art, following the teachings of the application, would produce AXY polymers falling within the scope of the claims. For instance, see Petit E, Caruelle JP[1] et al., *J. Biomacromolecules* 2004, which describes the synthesis of AXY polymers wherein A is glucuronan or glucoglucuronan. This article also discusses the tissue regenerating activities of sulfated glucuronan and glucoglucuronan AXY polymers using a rat *in vivo* model of injured muscle regeneration.

The specification also provides explicit teaching of know how to use the claimed AXY polymers to treat fibroses; see, *e.g.*, Example 12 (page 51) and Example 13 (page 57). Moreover, several post-filing publications show that the claimed AXY polymers can be used to treat or reduce fibrosis. For example:

- Desgranges P, Caruelle JP, Barritault D[2] et al., *FASEB.*, 1999 show that injury and disease such as ischemia and denervation after free whole skeletal muscle transplantation induce degenerative changes during the first week. For instance, transplanted *extensor digitorum longus* muscles in rats exhibit a large central zone of necrotic muscle fibers where the basal lamina may be completely degraded. This large central zone of necrotic muscle fibers is surrounded by a thin peripheral layer of surviving muscle fibers. A carboxymethyl benzylamide sulfonate dextran polymer inhibited the epimysial postinflammatory reaction and reduced the area of fibrotic tissue in the muscle fibers.

- Yamauchi H, Caruelle JP, Barritault D et al., *FASEB.*, 2000 shows that ischemia of cardiac muscle induces myocardial infarction and results in an irreversible loss of cardiac myocytes and necrosis. A dextran-derived AXY polymer reduced fibrotic tissue formation in pig hearts after experimentally-induced myocardial infarction.

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[1] Caruelle JP is a co-inventor of the present patent application.

[2] Barritault D is a co-inventor of the present patent application.

- Alexakis C, Caruelle JP, Barritault D et al., *Gut.*, 2004 showed that Crohn's disease is characterised by a collagenous fibrosis, and that an excess of fibrillar collagens occurs in all bowel wall layers. Dextran-derived AXY polymers (see Fig. 1 of this document) administered to human intestinal tissue *ex vivo* stimulated tissue repair and induced extracellular matrix remodelling by decreasing collagen production. These results indicated that polymers as presently claimed can be used in the treatment of intestinal fibrosis in Crohn's disease.

Thus, once an injury is made (ischemia, crush, incision, irradiation, etc.) the natural tissue response is to induce fibrosis. Fibrosis also occurs in chronic inflammatory conditions such as Crohn's disease, psoriasis, or pulmonary emphysemas. The present application shows, and the post-filing literature confirms, that fibrosis due to injury or chronic inflammation can be treated and reduced by administering the claimed AXY polymers.

The Examiner alleges that the specification is not enabling for claims reciting the "prevention" of fibrosis. The Applicants disagree; however, in the interests of advancing prosecution, the phrase 'and/or preventing' have been cancelled without prejudice from claim 42. The Applicants expressly reserve the right to pursue the cancelled subject matter in a continuing application.

The Office Action further alleges that the specification enables only on the *in vitro* administration of polymers of the series RGTA 1000-1025 and 1110-1115 to observe their effect on growth kinetics in smooth muscle tissue cultures or synthesis of collagens. According to the Office Action, the specfication does not provide actual guidance or evidence supporting the use of the claimed AXY polymers in treating or preventing fibroses in humans or animal models. The Applicants respectfully disagree.

The statements made in a patent application regarding how to make or use the claimed invention are assumed to be true, unless scientific evidence or cogent scientific reasoning as to why such statements are not true is presented. Here, the Office Action presents no such evidence or reasoning as to why the disclosed *in vitro* administration of the claimed AXY polymers could not be extrapolated to *in vivo* routes of administration.

In contrast, the specification teaches various *in vivo* routes of administration on pages 12-13, along with representative doses. The post-filing literature discussed above shows that the

claimed polymers do indeed treat and reduce fibrosis in animal models of muscle injury, muscle ischemia and denervation, and myocardial infarction. Thus, the teachings of the specification regarding *in vivo* administration are born out in the post-filing literature. The specification therefore adequately teaches the *in vivo* administration of the claimed AXY polymers.

One skilled in the art would know, from the teachings of the specification, how to make and use the AXY polymers of claims 42 and 61-62 (and new claims 63 and 64). These claims are therefore enabled by the specification, and the 35 U.S.C. 112, 1st paragraph enablement rejection of these claims should be withdrawn.

Claims 42 and 61-62 are rejected under 35 U.S.C. 112, 1st paragraph as allegedly lacking written description for all possible variations of the claimed AXY polymers. As discussed above, claim 42 has been amended to specify that A in the claimed AXY polymers is a monomer selected from the group consisting of a sugar or -(O-CH_2-CH_2-CO)-. New claim 63 has been added which specifies that the sugar is glucose.

The specification specifically discloses in Example 1, beginning on page 22, how to synthesize AXY polymers wherein :

- A is -(O-CH_2-CH_2-CO)-;
- X is -COOH or –COO^-Na^+; and
- Y is -CO-CH_2-CHOH-CH_2-SO_3H or -CO-CH_2-CHOH-CH_2-$SO^{3-}Na^+$.

Example 2, beginning on page 29, shows the synthesis of AXY polymers wherein:

- A is a glucose,
- X is -COOH or –COO^-Na^+
- Y is -SO_3H or -$SO^{3-}Na^+$.

Thus, the claimed AXY polymers, methods of their synthesis are expressly disclosed in the specification. The Applicants respectfully request that the written description rejection of claims 42 and 61-62 be withdrawn.

Response to the section 102(e) rejection

Claims 42 and 61-62 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by US Pat. No. 6,517,824 to Kohn et al. (Kohn). The Applicants respectfully traverse this rejection.

To anticipate a claim, a reference must disclose every element of that claim. Here, claim 42 as amended is directed methods of treating fibroses with a composition comprising an AXY polymer, in which A is a monomer selected from the group consisting of a sugar or -(O-CH_2-CH_2-CO)-. Kohn discloses a copolymer conjugate antifibrotic composition comprising a dipeptide. The polymer in the Kohn composition does not contain a monomer selected from the group consisting of a sugar or -(O-CH_2-CH_2-CO)-. Thus, Kohn does not disclose every element of claim 42 and its dependent claims 61-62 (and new dependent claims 63-64). The anticipation rejection of claims 42 and 61-62 should be withdrawn.

Conclusion

The Applicants respectfully submit that the entire application is now in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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